Excess of Nevi Related to Immunodeficiency: A Study in HIV–Infected Patients and Renal Transplant Recipients

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To assess the relationship between immune system and nevi, we studied two models of immunodeficiency caused by different mechanisms, i.e., virus and drug. Our rationale was that if an excess of nevi was found in these two epidemiologic models, it could be concluded that the excess was due to immunodeficiency itself rather than its cause. One hundred ten renal transplant recipients (RTR) were compared with age-, sex-, and phenotype-matched controls. Eighty four HIV-positive patients (HIV+) were compared with similarly matched controls. Nevi < 5 mm (N < 5) or ≥ 5 mm (N ≥ 5) were counted in three sites representative of regularly, intermittently, and never sun-exposed sites. The number of N < 5 was higher in RTR ($p < 0.001$) and in HIV+ ($p < 0.001$) than in respective controls. N ≥ 5 were significantly higher only in RTR. These differences tended to be the same for all sites and persisted after adjustment for possible confounding factors. The incidence of atypical nevus was higher in RTR than in controls.

Immunodeficiency seems to promote the occurrence of nevi. This supports the concept of immune surveillance of nevi and raises the question of whether sun-induced immune suppression plays a role in the development of nevi. As nevi are risk markers for melanoma, a higher incidence of melanoma could be expected in immunocompromised patients. ***Key words: melanoma/prevention/sun exposure. J Invest Dermatol 107:694–697, 1996***

Recent case control studies have shown that there is an excess of benign melanocytic nevi in long-term survivors of childhood cancer (Hughes *et al*, 1989; De Wit *et al*, 1990; Green *et al*, 1993) and in children with renal allografts (Smith *et al*, 1993). A possible explanation for these findings is that chemotherapeutic agents promote nevi, but it is also possible that the excess of nevi is due to immune depression.

Immune surveillance is a well-demonstrated concept for skin cancers (Fisher and Kripke, 1982). It is also accepted for melanoma (Ross, 1989), and host immune response provides a basis for new cancer therapies (Itoh *et al* 1992). Recent studies in renal allografts recipients and in survivors from childhood cancers raise the question of whether this concept also applies to nevus. Confirmation of a link between immune defect and number of nevi would have an important pathogenic implication with regard to the sun-induced development of nevi. Although the development of nevi is associated with sun exposure and fair complexion (Green and Swerdlow, 1989), the mechanisms of the promotion of nevus by sun radiation are not elucidated. Ultraviolet-induced immune suppression (Krutmann and Elmets, 1988) could be one of these mechanisms.

The influence of immune status on the development of melanocytic nevi is also important to predict the risk of cancer in immunocompromised patients because the number of nevi is the best risk factor for melanoma (Grob *et al*, 1990). With the increasing number and longer survival of immunocompromised patients, melanoma could become a problem.

To assess the relationship between immunodeficiency and the number of nevi, we studied two patient populations with immunodeficiency caused by completely different mechanisms, i.e., HIV-positive (HIV+) patients with a virus-induced immunodeficiency and renal transplant recipients (RTR) with a drug-induced immunodeficiency. Our rationale was that if both these epidemiologic groups had more nevi than controls, they would provide epidemiologic evidence that the excess of nevi was due to immunodeficiency itself rather than to the cause of immunodeficiency.

MATERIALS AND METHODS

Cases and Controls This multicenter study was conducted by the Réseau d' Epidemiologie en Dermatologie (RED) in six University hospitals in France: Brest, Colmar, Limoges, Marseille, Paris, and Tours. Two cross-sectional studies were performed simultaneously, one to compare RTR with matched controls (study 1) and the other to compare HIV+ patients with matched controls (study 2).

In the RTR study, eligible cases were randomly selected from RTR consulting at each transplant center. The only selection criteria were Caucasian phenotype and transplantation at least 2 y before. Controls were recruited either from "public health centers" where people from the general

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Abbreviations: RTR, renal transplant recipients; HIV+, HIV positive; N < 5, nevi < 5 mm; N ≥ 5, nevi ≥ 5 mm.

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Table I. No Significant Difference Between Renal Transplant Recipients and Controls with Regard to Age, Sex, Weight, and Sun Exposure

	RTR (110)[b]	Controls (110)[b]	p
Age	42.8 ± 11.2	42.7 ± 11.7	0.8
Sex	68M/42F	68M/42F	
Weight	65.3 ± 13.7	68.8 ± 13.8	0.06
Sun exposure[a]			
Vacations	2002 h ± 3093	2069 h ± 1839	0.84
Vacation at seaside	1662 h ± 3061	1604 h ± 1698	0.86
Leisure	1154 h ± 3201	1162 h ± 2251	0.55
Leisure at seaside	520 h ± 1240	491 h ± 1645	0.61
Occupational	145 days ± 542	345 days ± 2450	0.41

[a] Life cumulative sun exposure with uncovered back.
[b] Mean ± SD.

population are randomly called for check-ups or from hospital patients. Hospital patients admitted for skin disease, trauma (possible relation to outdoor activities and sun exposure), and chronic disease were excluded. Controls were matched with RTR with regard to age (± 5 y), sex, and hair color (red/blond, brown, black). In HIV+ study 2, eligible cases were randomly selected from HIV+ patients followed at each center. The only selection criteria was CD4+ lymphocyte count less than 400. Controls were recruited and matched in the same way as in the RTR study.

Nevus counts and interviews were performed at each center in cases and controls by the same dermatologist. These dermatologists were specially trained to apply the same counting technique. Any darkly pigmented lesion greater than 2 mm in diameter was counted as a melanocytic nevus if it was not considered to be any of the following: a freckle (poorly defined lesions, light to medium brown, less than 3 mm), a seborrheic keratosis (lusterless surface with patterned fine fissure or plugged follicular orifice), a solar lentigo (light brown pigmented lesions with irregular outlines located on exposed areas), a pigmented basal cell carcinoma, a pigmented actinic keratosis, or a pigmented dermatofibroma. Lentigo simplex was not excluded from counting because there are no absolute clinical criteria to distinguish it from junctional nevus and because lentigo is probably the earliest step in the ontogeny of nevi. Nevi were classified into two size categories: less than 5 mm in diameter ($N < 5$) and equal to or larger than 5 mm ($N \geq 5$). Atypical nevi were defined as $N \geq 5$ displaying at least two of the following criteria: irregular border, irregular color distribution, and asymmetry. Nevi were counted on three areas: on the left and right forearms, representative of regularly exposed areas; on the back, representative of intermittently exposed areas; and on the buttocks, representative of never exposed areas. Interviews were conducted with a standardized questionnaire recording successive places of residence, outdoor activities for leisure and vacation, occupational exposure, and use of tanning salons. Sun exposure was quantified by estimating the total cumulative number of hours spent outdoors with uncovered back for leisure, vacation, and/or occupation.

Statistical Analysis General characteristics of patients and total cumulative life sun exposure in cases and matched controls were compared by univariate paired analysis. Then number of nevi was compared by paired analysis of variance. When the total number of nevi was significantly different ($p < 0.05$) in patients and controls, the number of small nevi and large nevi were also compared separately. To take into account the potentially confounding factors, cumulative sun exposures expressed by quartiles of the distribution and weight were used in multivariate analysis also including age and sex (matching variables) as adjustment variables. As the distribution of nevi was not normal, the analyses were performed after logarithmic transformation. Paired analysis of variance and unconditional logistic regression were performed using BMDP statistical software, Inc. (Berkeley, CA).

RESULTS

There Is an Excess of Nevi in Renal Transplant Recipients A total of 110 RTR and 110 controls were enrolled in study 1. As shown in **Table I** the two groups were matched with regard to sun exposure and weight although weight was slightly lower in the RTR group. One hundred and six (96%) had been treated with cyclosporin A for 4.5 ± 1.8 y (range: 1.3–9) and 100 (91%) with azathioprin for 3.6 ± 2.1 y (range: 0.1–8). One hundred (91%) required dialysis for 3.2 ± 4 y (range: 0.1–20). Mean time from transplantation was 5.1 ± 3.1 y. Before and after adjustment for age, sex, weight, and sun exposure, the number of nevi was higher in RTR than controls **(Table II)**. This difference was significant for both $N < 5$ and $N \geq 5$ regardless of the site **(Table II)**. There was no significant difference between RTR and controls with regard to the number of atypical nevi whatever the site. It should be mentioned, however, that the number of patients with at least one atypical nevus was significantly higher in RTR than controls (29 *vs* 17, $p < 0.05$). Attempts to correlate number of nevi with time from transplantation or with type or duration of immunosuppressive drugs in renal transplant recipients were unsuccessful.

There Is an Excess of Nevi in HIV-Infected Patients Eighty four HIV+ patients and 84 controls were enrolled in the HIV+ study. The two groups were matched except with regard to weight **(Table III)**. Sixty-five patients (77%) had been treated with zidouudine and 28 (33%) with didanosine. Mean CD4+ lymphocyte count in patients was 102.3 ± 105.5. Before and after adjustment for age, sex, weight, and sun exposure, the number of small nevi ($N < 5$) was higher in HIV+ patients than controls **(Table IV)**. There was no significant difference in the number of larger nevi ($N \geq 5$) although this was probably due to their very low number. Number of small nevi was significantly higher in

Table II. Excess Nevi in Renal Transplant Recipients versus Controls

	RTR (110)[a]	Controls (110)[a]	Difference (95% Confidence Interval)	p crude/adjustment[a]
On the 3 sites				
Total number	**25.4** ± 24.2	**15.3** ± 11.3	+10.1 (5.4–14.7)	**< 0.001**/0.01
$n < 5$	23.2 ± 22.8	14.1 ± 10.7	+9.1 (4.8–13.4)	< 0.001/0.01
$n \geq 5$	2.2 ± 2.9	1.2 ± 2.1	+1 (0.4–1.6)	< 0.01/< 0.01
Back				
Total number	**16.0** ± 17.9	**9.2** ± 7.7	+6.8 (3.3–10.4)	**< 0.01**/< 0.05
$n < 5$	14.5 ± 16.8	8.1 ± 7.3	+6.4 (3.1–9.8)	< 0.05
$n \geq 5$	1.5 ± 2.5	1.0 ± 1.9	+0.5 (0.1–1.0)	< 0.05
Forearms				
Total number	**7.2** ± 8.8	**4.8** ± 4.9	+2.4 (0.6–4.2)	**< 0.01**/< 0.01
N< 5	6.7 ± 8.1	4.7 ± 4.7	+2.0 (0.4–3.7)	0.01
$n \geq 5$	0.5 ± 1.2	0.2 ± 0.5	+0.3 (0.1–0.4)	0.02
Buttocks	**2.2** ± 2.9	**1.4** ± 1.9	+1.2 (0.2–1.4)	**< 0.05**/0.05

[a] Mean ± SD.
[b] After adjustment for age, sex, weight, sun exposure.

Table III. No Significant Difference between HIV+ Patients and Controls as Regard to Age, Sex, and Sun Exposure, but a Lower Weight in HIV+ Patients

	HIV+ (84)[a]	Controls (84)[a]	p
Age	36.7 ± 7.9	36.3 ± 8.6	0.8
Sex	64 M/20 F	64 M/20 F	
Weight	59.7 ± 9.9	70.2 ± 13.8	< 0.001
Sun exposure[b]			
Vacations	2889 h ± 2555	2618 h ± 4226	0.6
Vacation at seaside	2576 h ± 2568	2352 h ± 4083	0.66
Leisure	940 h ± 2832	483 h ± 941	0.13
Leisure at seaside	575 h ± 2312	379 h ± 716	0.46
Occupational	38 days ± 122	54 days ± 196	0.52

[a] Mean ± SD.
[b] Life cumulative sun-exposure with uncovered back.

HIV+ patients than in controls, whatever the site. After adjustment, however, this remained significant only on the back **(Table IV)**. Patients and controls were not significantly different according to the number of atypical nevi whatever the site. The number of individuals with at least one atypical nevus was also not different in HIV+ patients and controls (11 *vs* 9). There was no significant correlation between the total number of nevi and immunodeficiency criteria, i.e., CD4+ lymphocyte count and severity of opportunistic infections on one hand, or between total number of nevi and treatment with zidouudine or didanosine (drug intake or length of treatment), on the other hand.

DISCUSSION

These two parallel cross-sectional studies showed that there was more melanocytic nevi in both the HIV+ and RTR groups than controls, although the excess was more clear-cut in RTR than HIV+ patients. It is unlikely that other factors influencing the number of nevi, such as age, sex, phenotype, and amount or type of sun exposure (Green *et al*, 1989; Richard *et al*, 1993), biased these results for two reasons. First, patients and controls were matched for age, sex, and hair color. Second, nevus counts were significantly higher in patients than in controls on differently exposed skin sites, even after adjustment for age, sex, weight, and sun exposure. Dermatologists who counted nevi knew the status of the patients or controls, but this potential bias probably did not play an important role because they applied a precise counting technique.

In HIV+ patients, the increase in the number of nevi may be attributed either to viral infection or immunodeficiency whereas in RTR it may be attributed either to renal failure, drugs, or immunodeficiency. The concordance of the results in these two populations with completely different mechanisms of immunodeficiency, however, suggests that the excess of nevi is due to immunodeficiency. Although these results do not rule out a possible direct effect of chemotherapeutic agents in the development of nevi, especially of the acral type (Green *et al*, 1993), they provide the first evidence that immunodeficiency itself can promote the development of nevi. We were unable to show a correlation between the number of nevi and parameters assessing severity of immunodeficiency such as CD4+ lymphocyte count and severity of opportunistic infections in HIV+ patients, on one hand, and time from transplantation or type of immunosuppressive drugs in RTR on the other hand. This apparent lack of correlation can be explained because all patients were severely immunocompromised with a CD4+ lymphocyte count under 400 in HIV+ patients (mean = 102.3) and a long history of drug-induced immunodeficiency in RTR (mean time from transplantation: 5.1 y). The fact that patients with less severe immunodeficiency were not enrolled in these studies makes it difficult to demonstrate a proportional relationship between number of nevi and degree of immunodeficiency.

Our results support the hypothesis of immune surveillance of nevi. There is much evidence that nevi are regulated by genetic factors, are correlated with phenotype markers (Gallagher *et al*, 1990b; Brogelli *et al*, 1991), and are promoted by sun exposure (Gallagher *et al*, 1990a; Richard *et al*, 1993). The immune system may also play a important role in the control of nevi. Because all melanoma in one group of renal allograft recipients arose from nevi (Greene *et al*, 1981) whereas fewer than one in five melanomas in normal persons do, Ross (1989) suggested that immune surveillance normally prevents melanoma from growing in or near nevi. He hypothesized that immune surveillance was able not only to kill or hold in check melanoma but was also able to control precursors by destroying nevi or limiting their growth. It is tempting to speculate that a defect in immune surveillance could also be implicated in the development of an excess of nevi in genetically predisposed individuals, as in "atypical mole" syndrome. In this regard, cases of eruptive dysplastic nevi have been reported in HIV+ patients (Duvic *et al*, 1989), and transplant recipients (Barker and Donald, 1988). We have to underline, however, that although more RTR than controls had at least one atypical nevi, there was no clear excess of atypical nevi in our patients.

The mechanisms by which sun exposure (Gallagher *et al*, 1990a; Richard *et al*, 1993) promotes the development of nevi are unknown (Pallowski *et al*, 1991). Ultraviolet-induced DNA damage might be involved (Miller, 1985) but may not be the only explanation. It has been widely demonstrated that exposure to ultraviolet light affects the ability to eliminate infectious pathogens, reject skin cancer, and mount both delayed-type hypersensitivity and contact hypersensitivity reactions (Krutmann and Elmets, 1988; Roberts *et al*, 1989, Goettsch *et al*, 1993). Our epidemiologic data raise the possibility that ultraviolet-induced immune suppression could be one of the mechanisms by which sun exposure causes an increase in the number of nevi.

Immunocompromised patients are at higher risk for skin tumors. In this regard skin carcinoma is more frequent in transplanted

Table IV. Excess of Nevi in HIV+ Patients versus Controls

	HIV (84)[a]	Controls (84)[a]	Difference (95% Confidence Interval)	p Crude/Adjustment[b]
On the 3 sites				
Total number	**21.5** ± 20.4	**13.1** ± 13.1	+8.4 (3.7–13.1)	**< 0.001/< 0.001**
n < 5	20.6 ± 18.2	12.3 ± 12.5	+8.3 (3.7–12.9)	< 0.001/< 0.001
n ≥ 5	0.8 ± 1.4	0.8 ± 1.4	0 (−0.4–0.5)	0.48/0.70
Back				
Total number	**14.9** ± 14.5	**8.6** ± 9.6	+5.7 (2.9–9.7)	**< 0.001**/< 0.001
n < 5	14.2 ± 14.2	8.0 ± 9.1	+6.2 (5.3–9.1)	< 0.01
n ≥ 5	0.7 ± 1.4	0.7 ± 1.3	0 (−0.3–0.4)	0.4
Forearms	**5.1** ± 5.9	**3.8** ± 4.1	+1.3 (−0.11–2.8)	**0.03**/0.4
Buttocks	**1.5** ± 2.6	**0.7** ± 1.0	+0.6 (0.3–1.4)	**< 0.01**/< 0.3

[a] Mean ± SD.
[b] After adjustment for age, sex, weight, sun exposure.

patients, and Kaposi's sarcoma is more frequent in both transplanted patients and HIV+ patients (Walz *et al*, 1992; Sheil *et al*, 1993). The fact that we also observed an excess of melanocytic nevi, which are the most important risk factors of melanoma (Grob *et al*, 1990) and its only known precursor, suggests that immunocompromised patients may also be at higher risk for melanoma. Melanoma has already been reported in graft recipients (Vilardell *et al*, 1992), in HIV+ patients (Tindall *et al*, 1989), and after Hodgkin disease (Tucker *et al*, 1985). An excess of melanoma has even been described in transplant recipients (Birkeland *et al*, 1975). In a recent collaborative European study from several transplant centers, however, the incidence of melanoma in 25,914 females was only 16 as compared to an expected incidence of 12 (Stewart *et al*, 1995). Because the incidence and the delay of occurence of cancers in immunocompromised patients varies according to the type of tumor and may depend on age of onset and length of immune suppression, the excess of nevi observed in both transplanted and HIV+ patients suggests that further studies are warranted to evaluate the long-term risk of melanoma.

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